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Learning System

Module 3:
Focus on Opioids

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Focus on Opioids

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Introduction

Opioids have been the mainstay of pain treatment for thousands of years.[1] Morphine, the classic opioid, has long been known to be effective in relieving severe pain.[2] Morphine is derived from opium, which is found in the poppy seed.[2] Morphine was first isolated from opium in 1803, and was named after the Greek god of dreams, Morpheus.[2] The term opioid refers to all compounds that are related to opium, and may include natural products like morphine that are derived from opium as well as several semisynthetic derivatives.[1] You may also encounter the term "narcotic"; however, this is a term more related to legal aspects of drugs of abuse.[3,4] Throughout this learning system we use the term "opioid" because it is the medically accepted term, and you should also use "opioid" in your conversations with healthcare professionals.

You will need to have a thorough understanding of opioids in general as well as specific agents in order to discuss the treatment of chronic moderate to severe pain with healthcare professionals. This module is designed to provide you the information you need.

- The discussion begins by describing how opioids provide pain relief and how they affect many organ systems in the body.
- Opioids can be classified in several different ways based on their features, and section 2 discusses these features.
- Because the focus of this learning system is on pain relief for chronic moderate to severe pain, section 3 provides profiles of the opioids that are available in extended-release formulations.

The module is designed to facilitate your learning of this information. Each section begins with learning objectives that identify the goals of the section. The progress check questions at the end of each section are based on the learning objectives and allow you to check your understanding of the information. Throughout the module, glossary terms are defined in the margin and these definitions are also available in an end glossary. The module concludes with a summary and an appendix of opioid risk assessment tools available to physicians.

1: Physiologic Effects of Opioids

Introduction

The primary reason opioids are administered is to provide **analgesia**—that is, to reduce the perception of pain.[4] In fact, opioids are the most potent pain-relieving medications available.[5] This section describes how opioids provide pain relief by binding to opioid receptors. In addition to pain relief, opioids also produce effects in a wide range of body systems, which are also discussed in this section.

analgesia (an′ăl-jē′zē-ă): relief of pain

Learning Objectives

Upon completion of this section, you should be able to:

- List and describe the 3 key opioid receptors, with an emphasis on the mu (μ) receptor
- Describe the mechanism through which opioids reduce the perception of pain
- Describe the physiologic effects of opioids

1.1 Opioid Receptors

As you learned in prior modules, endogenous opioid compounds such as **endorphins** and **enkephalins** prevent pain impulses by binding to opioid receptors.[6,7] Opioid receptors are located throughout the **central nervous system (CNS)** and **peripheral nervous system (PNS)**.[1,7] Three types of opioid receptors are known to be involved in analgesia[4]:

- mu (μ) opioid receptors
- delta (δ) opioid receptors
- kappa (κ) opioid receptors

endorphins (en-dōr′finz): group of endogenous opioid peptides in the body

enkephalin (en-kef′ă-lin): a type of endorphin, which are endogenous opioid peptides in the body

central nervous system (CNS) (sen′trăl ner′vūs sis′tēm): the brain and the spinal cord

peripheral nervous system (PNS) (pĕ-rif′ĕr-ăl): all nervous system tissue except for the brain and spinal cord

While all of these receptors have a role in pain relief when endogenous opioids bind to them, most of the clinically available opioid medications act primarily by binding to μ receptors.[1] There are 2 μ receptor subtypes[4]:

- μ-1 receptors, which are thought to be responsible for the analgesic properties of opioids
- μ-2 receptors, which are thought to be responsible for some of the other physiologic effects of opioids, including key adverse effects

1.2 Opioid Mechanism of Action

Although opioid receptors are located in both the CNS and PNS, opioids produce analgesia by binding to μ opioid receptors in the CNS.[5] On the cellular level, binding to μ receptors[2]:

- closes calcium channels on presynaptic neurons, which reduces neurotransmitter release
- opens potassium channels on postsynaptic neurons, which makes it more difficult for an impulse to be created

From a larger perspective, these actions mean that[5]:

- in the brain, opioids activate neurons that inhibit pain impulses
- in the spinal cord, opioids inhibit neurons that transmit pain impulses

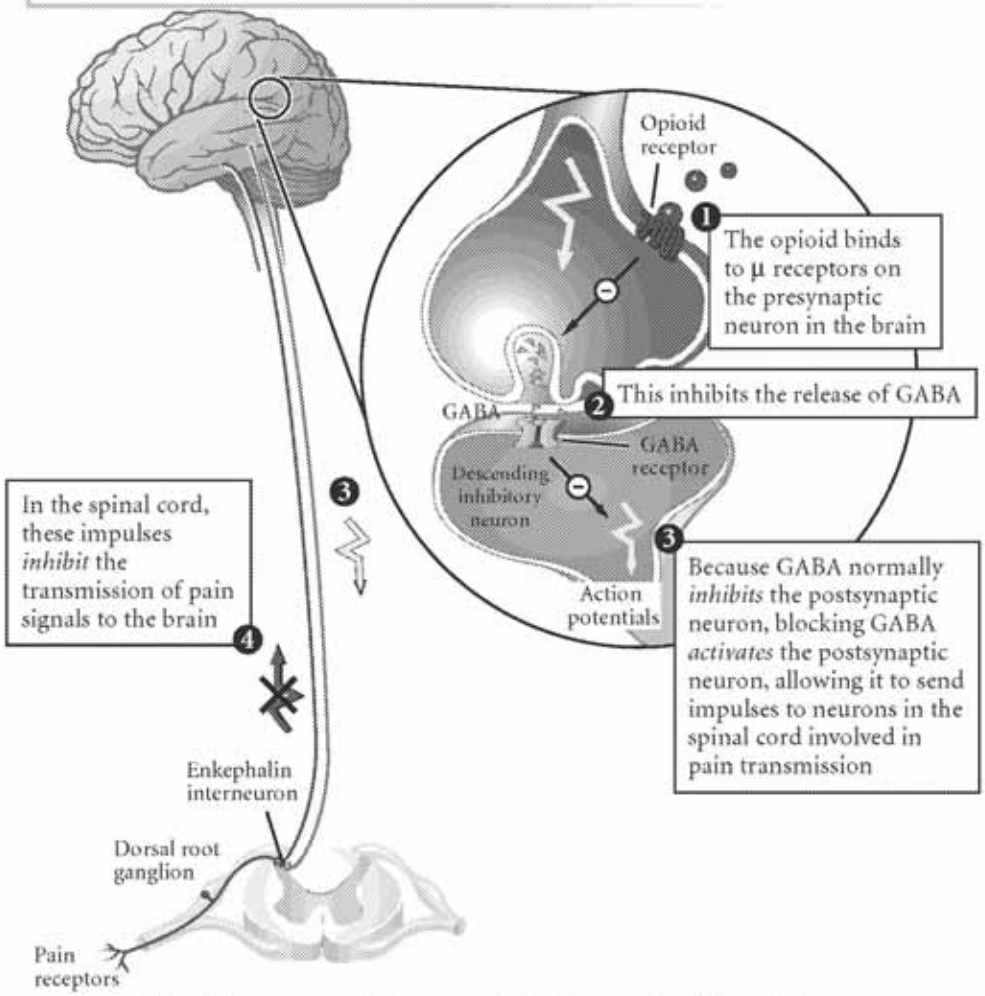
Opioids Activate Neurons That Inhibit Pain Impulses

As you learned in the *Overview of Pain* module, when the brain receives an impulse, it can quickly send a response to the spinal cord that inhibits the transmission of additional pain signals.[6,7] As shown in Figure 1A[2]:

1. the opioid binds to μ receptors on a presynaptic neuron in the brain
2. this *inhibits* the release of the neurotransmitter **gamma-aminobutyric acid (GABA)**
3. because GABA normally *inhibits* the postsynaptic neuron, blocking GABA *activates* the postsynapatic neuron, allowing it to send impulses to neurons in the spinal cord involved in pain transmission
4. in the spinal cord, these impulses *inhibit* the transmission of pain signals to the brain

gamma-aminobutyric acid (GABA)
(gam′ă ă-mē′nō-byū-tir′ĭk as′id):
a major inhibitory neurotransmitter in the brain

Figure 1A: Opioids Activate Neurons That Inhibit Pain Impulses[1,2,8]



Adapted from Katzung, 2007; Brunton et al, 2006; Tortora and Derrickson, 2009.

Opioids Inhibit Neurons That Transmit Pain Impulses

Opioids can also bind to μ receptors on neurons in the dorsal horn of the spinal cord, and this directly inhibits the transmission of pain signals to the brain.[2] As shown in Figure 1B[1,2]:

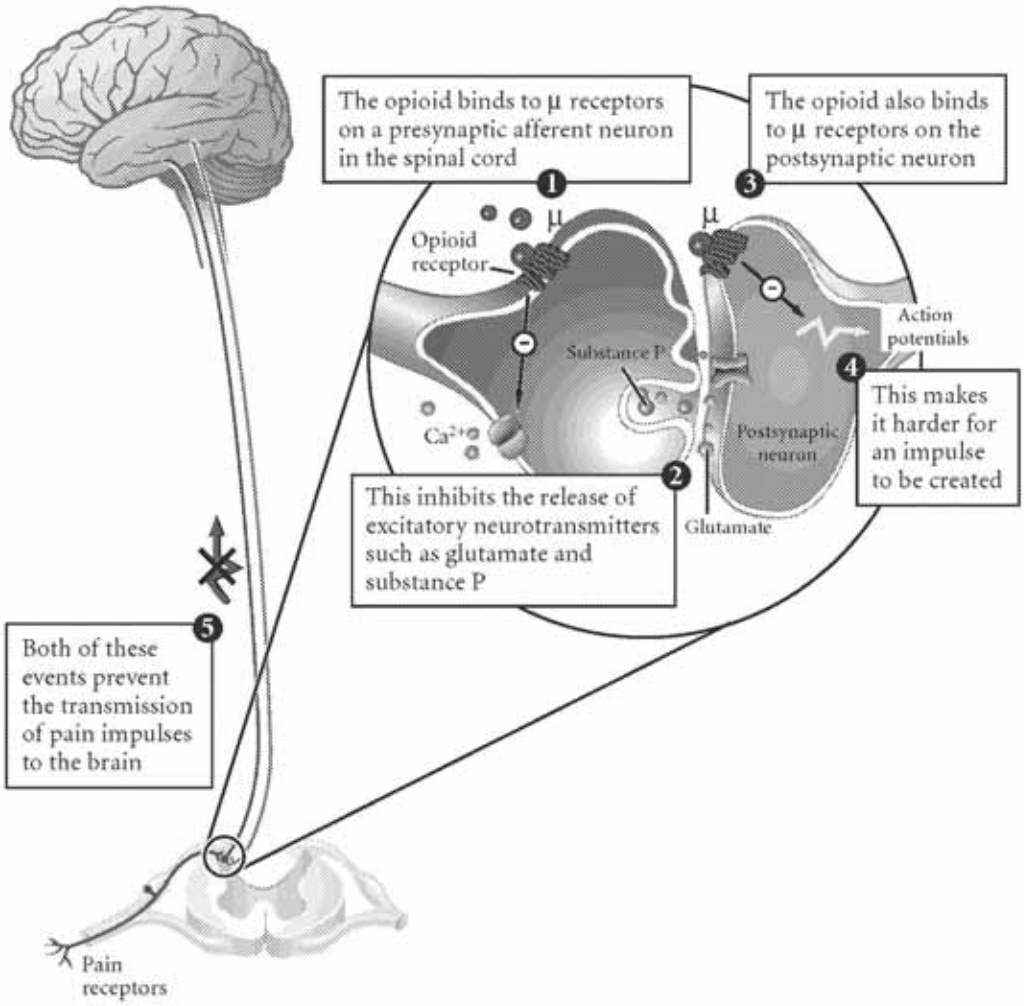
1. the opioid binds to μ receptors on a presynaptic **afferent neuron** in the spinal cord
2. this inhibits the release of excitatory neurotransmitters such as **glutamate** and **substance P**
3. the opioid also binds to μ receptors on the postsynaptic neuron
4. this makes it harder for an impulse to be created
5. both of these events prevent the transmission of pain impulses to the brain

afferent neurons (af′ĕr-ĕnt nū′rons): also called sensory neurons; detect and/or transmit information from the PNS to the CNS

glutamate (glū′tă-māt): a major excitatory neurotransmitter

substance P (sŭb′stănts): neurotransmitter found in inflamed tissue and involved in pain transmission

Figure 1B: Opioids Inhibit Neurons That Transmit Pain Impulses[1,2,8]



Adapted from Katzung, 2007; Brunton et al, 2006; Tortora and Derrickson, 2009.

1.3 Physiologic Effects of Opioids

As discussed in the following paragraphs, in addition to providing pain relief, opioids also produce a variety of other physiologic effects.[1] Some of these effects, such as pain relief and respiratory depression, occur due to binding to μ receptors in the CNS; some effects, such as constipation, occur due to binding to μ receptors in the PNS; and some effects, such as nausea and vomiting, are mixed effects.[2,3,5]

Pain Relief

Opioids are the most potent pain-relieving drugs available, and morphine remains the standard against which strong analgesics are compared.[2,5] Patients with pain who receive treatment with opioids often report that their pain has become less intense or nonexistent.[1] In general, continuous and dull pain is relieved more effectively than sharp or intermittent pain.[1] Opioids are unique in that they are able to diminish both the physical and emotional components of pain.[2] Patients sometimes report that while some pain is still present, they feel more comfortable.[1]

Respiratory Depression

Opioids can affect respiration by decreasing the breathing rate and the depth of each breath.[4] Respiratory depression is conventionally defined by a respiration rate of <12 breaths per minute.[9] Respiratory depression occurs because opioids inhibit the brain's respiratory center, a group of neurons that controls breathing.[1,2,6]

Respiratory depression is dose-related, increasing as the dose of opioid is increased.[1] Respiratory depression is rarely clinically significant in patients who are otherwise healthy and taking typical therapeutic doses.[4] However, it can be more serious in some patients, such as those with increased intracranial pressure, those with pulmonary medical conditions such as asthma, or those receiving **supra-therapeutic doses**.[1,2]

Euphoria and Dysphoria

Patients taking opioids may experience **euphoria**, or a pleasant "floating" sensation and feel less anxious and distressed.[2] However, **dysphoria**—an unpleasant state characterized by restlessness and uneasiness—may also occur in some patients.[2] It is not known exactly how opioids produce euphoria, but the pathways involved are thought to be different from those involved in pain relief.[1]

supra-therapeutic dose: a dose greater than that needed to produce a desired effect

euphoria (yū-fôr′ē-ă): a feeling of pleasure or well-being, commonly exaggerated and not necessarily well-founded; may be induced by a drug or substance of abuse

dysphoria (dis-fôr′ē-ă): mood of general dissatisfaction, restlessness, depression, and anxiety; a feeling of unpleasantness or discomfort

Miosis

miosis (mī-ō′sis): constriction of the pupil of the eye, resulting from a normal response to an increase in light or caused by certain drugs or pathologic conditions

Miosis, or constriction of the pupils of the eye, occurs with almost all opioids.[2]

Sedation, Drowsiness, and Cognitive Effects

Sedation and drowsiness are common occurrences with opioid treatment, especially when therapy is initiated or when the dose is significantly increased.[2,3] Patients should be forewarned about the potential for sedation with initial use, and encouraged to avoid certain activities such as driving.[3] Issues with sedation may persist if other factors are also present, such as the use of other sedation-inducing medications or dementia.[3] Sleep is more likely to be induced in the elderly than in young and healthy individuals, although the individual can usually be aroused easily from this sleep.[2] Drowsiness is also a common effect of opioids.[2] Clouded thinking and mild cognitive impairment can also occur with opioids.[2,3]

Cough Suppression

The cough reflex is triggered when nerve impulses from the respiratory passages are transmitted to the cough center in the brain, causing the individual to cough.[1,6] Opioids depress the cough center and can thus suppress coughing.[1] This can be a therapeutic effect, but it can also lead to the accumulation of respiratory secretions and, in turn, to airway obstruction.[2]

Gastrointestinal Effects

When opioids bind to peripheral opioid receptors in the gastrointestinal (GI) tract, it slows gastric emptying time by decreasing the wave-like movements of the intestine.[4] This can lead to constipation.[4] Constipation is the most common adverse effect of chronic opioid therapy, with most patients developing some degree of constipation when therapy starts or the dose is increased.[2,3,10] Constipation does not diminish with continued use of the opioid.[2,3]

Urinary Retention

urinary retention (yūr′i-nār′ē rē-ten′shūn): the keeping of urine in the body that should normally be discharged

Opioids can depress urinary function.[2] They not only inhibit the urinary voiding reflex but they also increase the smooth muscle tone of the ureter and bladder—which allows for additional urine to collect in the bladder—and these effects can precipitate **urinary retention.**[1-3]

Pruritus

The **pruritus** (itching) that can occur with opioid use is thought to be due to opioid effects in the CNS as well as opioid influence on release of **histamine** in the skin.[2] Pruritus is more common when opioids are administered **parenterally**.[2]

Nausea and Vomiting

Opioid-induced nausea and vomiting are thought to be mediated by opioid receptors in both the CNS and PNS.[3] In the brain, opioids stimulate the vomiting center.[1] In the PNS, the actions of opioids on the GI tract, such as decreasing gastric motility and delaying gastric emptying, are thought to play a role.[3]

pruritus
(prū-ri′tūs):
itching

histamine
(his′tă-mēn):
a monoamine neurotransmitter; in the periphery, it is released from cells in the immune system; it also stimulates gastric secretion and the constriction of bronchial smooth muscle

parenteral
(pă-ren′tĕr-ăl):
administration by some other route than through the gastrointestinal tract; particularly refers to administration via injection

Summary

The following table summarizes the information presented in this section.

Physiologic Effects of Opioids
▪ The 3 types of opioid receptors known to be involved in analgesia are: – μ opioid receptors – δ opioid receptors – κ opioid receptors ▪ Most clinically available opioids produce analgesia primarily by binding to μ receptors in the CNS – the effects associated with opioid binding at μ receptors include analgesia as well as other physiologic effects
▪ When opioids bind to μ opioid receptors, they close calcium channels on the presynaptic neuron (reducing the release of neurotransmitters) and open potassium channels on the postsynaptic neuron (making it more difficult for an impulse to be created) ▪ These actions mean that: – in the brain, opioids activate neurons that send inhibitory signals to neurons in the spinal cord – in the spinal cord, opioids inhibit neurons that transmit pain impulses from the spinal cord to the brain
▪ Key physiologic effects of opioids include: – opioids are the most potent pain-relieving drugs available, and morphine remains the standard against which strong analgesics are compared – opioids can cause respiratory depression by decreasing the breathing rate and depth of each breath in a dose-related fashion; rarely clinically significant in otherwise healthy people taking typical therapeutic doses – patients can experience euphoria or dysphoria – miosis occurs with almost all opioids – sedation, drowsiness, and cognitive effects are common, especially when therapy is initiated or the dose is increased – the cough reflex can be suppressed – opioids decrease the wave-like movements of the intestine, which slows gastric emptying time, which may result in constipation – opioids inhibit the urinary voiding reflex and increase smooth muscle tone of the ureter and bladder, which can result in urinary retention – pruritus can occur due to opioid effects in the CNS as well as because of peripheral histamine release – nausea and vomiting can occur due to opioid stimulation of the brain's vomiting center and effects in the GI tract

Progress Check

There may be **more than one** answer for each question.

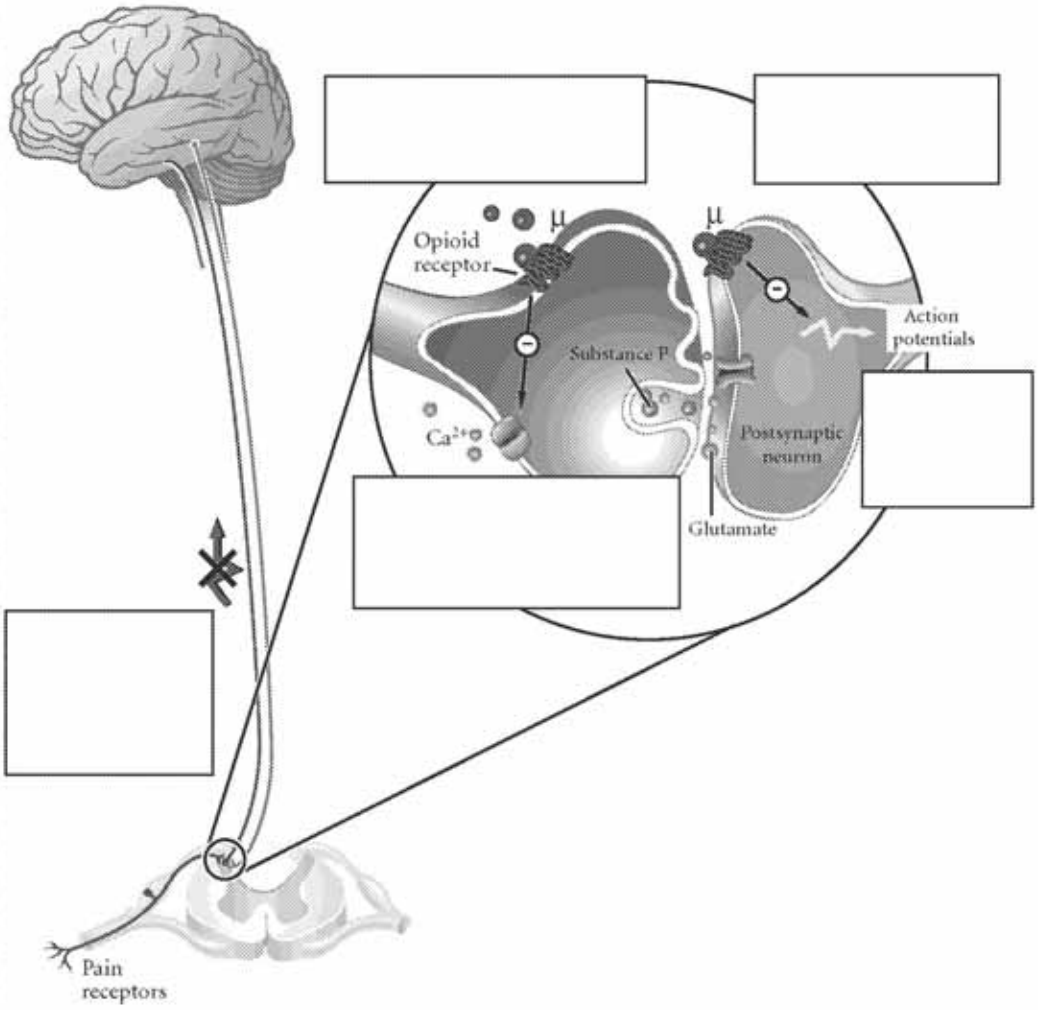
1. Most of the clinically available opioid medications act primarily by binding to ___ receptors in the ____.

2. Fill in the blanks in the following statements, selecting from the following options: opens; closes; potassium; chloride; calcium; presynaptic; postsynaptic; reduces; increases; makes it easier; makes it more difficult

   A Binding to μ receptors closes _____ channels on _____ neurons, which _____ neurotransmitter release.

   B Binding to μ receptors _____ potassium channels on _____ neurons, which _____ for an impulse to be created.

3. Use the following to label the illustration:
   - This makes it harder for an impulse to be created
   - Opioid binds to μ receptors on a presynaptic afferent neuron in the spinal cord
   - Opioid binds to μ receptors on the postsynaptic neuron
   - Both of these events prevent the transmission of pain impulses to the brain
   - This inhibits the release of excitatory neurotransmitters such as glutamate and substance P



Adapted from Katzung, 2007; Brunton et al, 2006; Tortora and Derrickson, 2009.

4. In terms of pain relief:

   A opioids relieve sharp pain more effectively than continuous and dull pain.

   B opioids are unique in that they primarily relieve the emotional component of pain.

   C morphine remains the standard against which strong analgesics are compared.

   D opioids produce their effects by binding to receptors in the CNS.

5. Which of the following statements about the physiologic effects of opioids is (are) **true**?

   A The incidence of respiratory depression is dose-related.

   B Sedation is most likely to occur as a withdrawal symptom, when the opioid dose is decreased.

   C Constipation is the most common adverse effect of chronic opioid therapy.

   D Patients taking opioids may experience euphoria, a pleasant "floating" sensation.

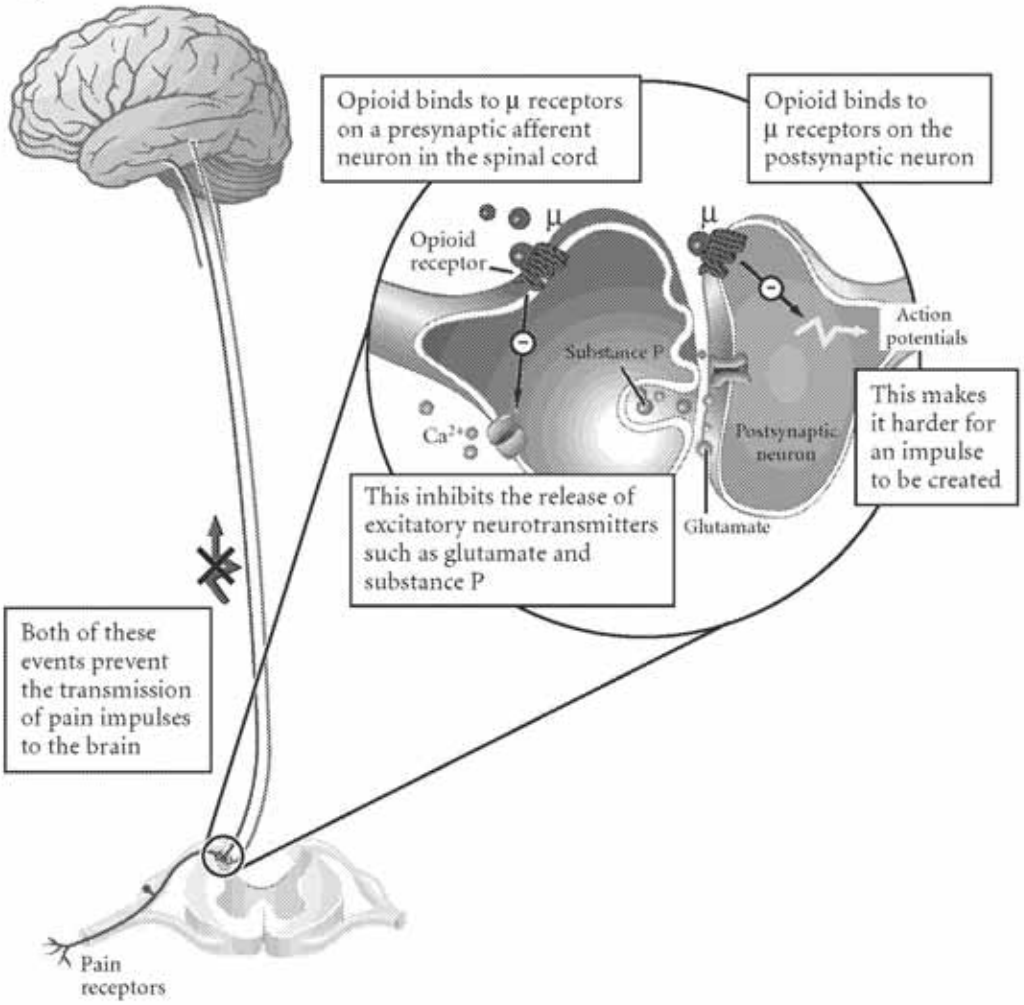
Answers

1. μ; CNS

2. A Binding to μ receptors closes calcium channels on presynaptic neurons, which reduces neurotransmitter release.

   B Binding to μ receptors opens potassium channels on postsynaptic neurons, which makes it more difficult for an impulse to be created.

3.



Adapted from Katzung, 2007; Brunton et al, 2006; Tortora and Derrickson, 2009.

4. C, D

5. A, C, D

2: Opioids in Clinical Use

Introduction

Opioids can be classified in a variety of ways based on fe atures such as potency, formulation, onset and duration of action, and potential for abuse. When choosing an opioid for an individual patient, a physician considers these drug-related factors as well as the patient's circumstances. This section describes features of opioids and how opioids are classified based on these features.

Learning Objectives

Upon completion of this section, you should be able to:

- Differentiate among opioid agonists, opioid partial agonists, opioid antagonists, and mixed opioid agonist-antagonists
- Define equianalgesic dose and morphine equivalent and describe how this concept relates to potency
- Describe the different routes of administration for opioids
- State the key factor in onset of action of opioids
- Differentiate between short-acting and long-acting opioids
- Differentiate among tolerance, physical dependence, and addiction and explain the 5 schedules for controlled substances
- List several opioid risk assessment tools and describe how they are used
- Compare key features of short-acting and long-acting opioids

2.1 Types of Opioids

As noted in the following table, opioids can be categorized based on their interaction with opioid receptors.[3]

Types of Opioids[1,3]

Type	Description	Examples
Opioid **agonists**	▪ Bind to opioid receptors and stimulate them, producing analgesia ▪ Have no "**ceiling**" in analgesia; this means that analgesic effects increase as the dose is increased	▪ Morphine, hydromorphone, oxycodone, hydrocodone, codeine, fentanyl
Opioid **partial agonists**	▪ Bind to opioid receptors and stimulate them, producing analgesia, but have less activity compared to full agonists ▪ Have a ceiling effect: increasing the dose above its ceiling does not result in any further increase in analgesia	▪ Buprenorphine
Opioid **antagonist**	▪ Bind to opioid receptors and block the binding and action of agonists at the receptor ▪ May be used therapeutically to treat opioid adverse effects (eg, respiratory depression)	▪ Naloxone, naltrexone
Mixed opioid agonist-antagonist	▪ Bind to and produce agonist effects at one type of opioid receptor and antagonist effects at another type of opioid receptor	▪ Pentazocine

agonist
(ag′on-ist):
a drug capable of initiating drug actions by combining with a receptor

ceiling effect:
occurs when increasing the dose of a drug above a certain point does not produce a further increase in response

partial agonist
(ag′on-ist):
an agent that binds to receptors and stimulates them, but has less activity compared to a full agonist

antagonist
(an-tag′ō-nist):
a drug that binds to receptors and blocks the binding and action of agonists at the receptor

Only opioids with agonist effects (either agonists or partial agonists) produce pain relief.[4] Physicians choose among the various opioids that are available for pain relief based on factors such as[1]:

- potency
- route of administration
- onset and duration of action
- potential for abuse

If patients experience intolerable adverse effects and/or inadequate pain relief with a specific opioid, physicians usually switch them to another opioid to achieve the appropriate balance between pain relief and adverse effects.[3]

2.2 Potency

One way in which opioids are grouped is in terms of their potency. Traditionally, morphine has been considered the standard against which all other opioids are compared.[1,11] That is, the dose is determined that is needed to produce the same amount of pain relief as morphine 10 mg administered parenterally or 30 mg or 60 mg administered orally.[1,11] This is called the **equianalgesic** dose or morphine equivalent.[1,11]

equianalgesic (ē′kwē-anal-jē′zik): the dose of a drug needed to produce the same amount of pain relief as a 10 mg intravenous or a 30 mg oral dose of morphine; often termed a morphine equivalent

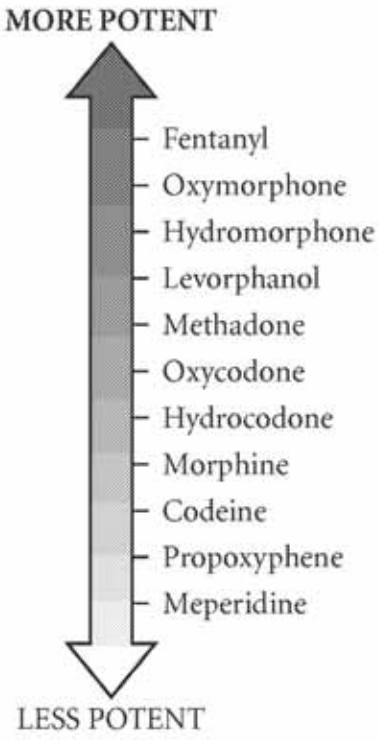
Data from studies of patients with pain have been used to develop equianalgesic dose tables for opioids.[3] For example, the equianalgesic dose of oral hydromorphone is commonly accepted as 6 mg (based on a 30 mg oral dose of morphine and a 5:1 morphine:hydromorphone conversion ratio).[12] However, it is important to note that the information provided in these dose tables is not meant to represent standard doses or absolute guidelines for dose selection, for the information varies from table to table.[3,13] Instead, dosing must be individualized for each patient to ensure the optimal balance between pain control and adverse effects.[3,13]

Historically, the potency of opioids has also been described qualitatively as "weak" or "strong."[3] This distinction was not based on pharmacologic differences, but rather on the manner in which the drugs were used[3]:

- an opioid that was used to treat mild to moderate pain was referred to as a weak opioid
- an opioid that was used to treat moderate to severe pain was referred to as a strong opioid

Figure 2A presents the relative potency of selected opioids. As shown, according to oral equianalgesic doses, hydromorphone is more potent than morphine.[1]

Figure 2A: Relative Potency of Selected Opioids[1,14]



Adapted from Brunton et al, 2006; Periyakoil et al, 2008.

2.3 Route of Administration

Opioids may be administered by various routes, as listed in the following table.

Routes of Administration[1,3,11]

Route	Description
Oral (tablets, capsules, solutions)	• Often the most appropriate choice in routine practice
Transmuscosal: buccal, sublingual, and nasal	• Absorbed through the mucosal membrane of the oral cavity (cheek or under the tongue) or the nasal cavities
Parenteral	• Administration other than through the GI tract; appropriate for those who cannot use oral routes, need rapid onset of analgesia, or who need high doses that cannot be administered by other routes: – intravenous injection: into a blood vessel – intramuscular injection: into a muscle – subcutaneous injection: beneath the skin • Can be given as a **bolus** injection or as a continuous infusion
Transdermal	• Absorbed through the skin from a patch that slowly releases the drug
Rectal	• Absorbed through the rectal mucosa; provides potency roughly equal to oral administration

bolus
(bō′lŭs):
a single, relatively large quantity of a drug

As noted in a prior module, some opioids may be administered in combination with nonopioid analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs).[3,4] The coadministration of an opioid and a nonopioid agent may provide additive or even **synergistic** analgesic effects.[3,5] The enhanced efficacy of the combination allows physicians to reduce the dose of the opioid, which in turn can reduce the incidence of any dose-related adverse effects associated with the opioid.[3,5] However, a fixed-dose combination that contains an opioid and acetaminophen may pose a risk for patients who find it necessary to increase their dose of medication, as higher than recommended doses of acetaminophen may be toxic to the liver.[5]

synergism
(sin′ĕr-jĭzm):
coordinated or correlated action of 2 or more structures, agents, or physiologic processes so that the combined action is greater than the sum of each acting separately

2.4 Onset and Duration of Action

Onset of Action

The onset of action of an opioid is primarily dependent upon the route of administration.[5]

- The most rapid relief is obtained by intravenous administration, while the onset of action with oral agents is much slower because they need to go through the GI tract before they reach the bloodstream.[5]
- The transmucosal formulation also provides a rapid onset of action because the agent bypasses the GI system.[3,11] Fentanyl is available as a lozenge on a stick that is rubbed against the inside of the patient's cheek until it has dissolved.[3] The time to onset of analgesia with transmucosal fentanyl is 5 to 15 minutes.[3,15] This formulation has been shown to be particularly useful in the management of breakthrough pain, which is a brief period of exacerbated pain during which the patient's usual opioid regimen fails to provide adequate pain relief.[3]
- Orally administered agents have a slower onset than parenterally administered agents; extended-release oral formulations have a slower onset than immediate-release oral formulations.[3]
- In contrast, the transdermal formulation of fentanyl has a slower onset of action, with concentrations of the drug increasing gradually over several hours.[3]

Duration of Action: Short-Acting Versus Long-Acting Opioids

Duration of action is also an important consideration when selecting an opioid for the treatment of pain.[1] Opioids are often classified as short-acting or long-acting opioids.[1,4]

prn: as needed (from the Latin for *pro re nata*, which means as the occasion arises)

A short-acting opioid may be the appropriate choice when "as-needed" (or **prn**) pain relief rather than "around-the-clock" pain relief is required, such as during a short but painful medical procedure.[1,4] Short-acting opioids are commonly used during the initial phase of opioid treatment, as it is easier to resolve the medication's unexpected or intolerable adverse effects should they occur.[4]

A long-acting opioid may be used when less frequent dosing is preferred.[1] In reality, methadone is the only intrinsically long-acting opioid.[3] Because levorphanol has a long half-life, some physicians also consider levorphanol intrinsically long acting.[3] However, some short-acting opioids—such as morphine, oxycodone, oxymorphone, and fentanyl—are formulated in delivery systems that increase their duration of action, making them long-acting agents.[3,16]

The following table presents examples of short-acting and long-acting opioids.

Duration of Action of Commonly Used Opioids[3,16]	
Short-Acting	Long-Acting
▪ Codeine ▪ Fentanyl (including transmucosal formulation) ▪ Hydrocodone ▪ Hydromorphone ▪ Levorphanol ▪ Meperidine ▪ Morphine ▪ Oxycodone ▪ Oxymorphone ▪ Propoxyphene	▪ Fentanyl, transdermal ▪ Methadone ▪ Morphine, sustained-release ▪ Oxycodone, sustained-release ▪ Oxymorphone, sustained-release

Hydromorphone

Hydromorphone, a short-acting opioid, is only available in an immediate-release formulation in the United States.[3]

Outside the United States, an extended-release formulation of hydromorphone, Jurnista™, was recently approved for the treatment of severe pain.[17] Jurnista™ has a delivery system that utilizes the OROS® Push-Pull™ osmotic pump technology.[18,19] This system helps ensure constant delivery of hydromorphone over a 24-hour period.[20]

An extended-release formulation of hydromorphone using a different delivery system was also briefly on the market in the United States. This agent, branded as Palladone™, was approved in 2004 for the management of persistent moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high-potency opioid for an extended period of time.[21,22] Hydromorphone was formulated as pellets in a controlled matrix release system.[22] However, soon after the product's approval, a pharmacokinetic study in healthy subjects showed that coingestion of the drug with alcohol resulted in significant increases in the concentration of hydromorphone, which could have fatal effects.[21] In 2005, Purdue Pharma agreed to voluntarily suspend sales and marketing of Palladone™ in the United States.[23]

2.5 Potential for Abuse

Because of their effects in the CNS, opioids can have a reinforcing capacity (produce effects that make an individual wish to take them again).[1] When in combination with individual patient and environmental factors, a drug with reinforcing qualities has the potential for[10]:

- misuse: the use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not
- abuse: any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose, such as altering one's state of consciousness
- diversion: the intentional transfer of a controlled substance from legitimate distribution and dispensing channels

The following paragraphs describe the physiological and psychological concepts involved in the potential for abuse.

Tolerance, Physical Dependence, and Addiction

The following terms are used to describe some potential consequences of opioid use, and it is important to distinguish among them:

- tolerance
- physical dependence
- addiction

tolerance (tol′ĕr-ăns): the effectiveness of the drug diminishes over time, and a higher dose is necessary to produce the same effect that was previously attained at a lower dose

physical dependence: the body's normal adaptation to the opioid, and the body requires continued drug administration in order to function normally

hyperventilation (hī′pĕr-ven′ti-lā′shŭn): increased pulmonary rate that is greater than necessary for gas exchange; can lead to dizziness, fainting, psychomotor impairment

Tolerance means that the effectiveness of the drug diminishes over time, and a higher dose is necessary to produce the same effect that was previously attained at a lower dose.[24] Tolerance is a common response to the repetitive use of an opioid.[1] However, tolerance does not occur equally to all the effects of an opioid—while tolerance may develop for the analgesic and sedating effects, tolerance seldom develops for miosis and constipation.[2]

Physical dependence is the body's normal adaptation to the opioid, and the body requires continued drug administration in order to function normally.[1,24] If the patient stops the drug abruptly, withdrawal symptoms occur.[24] The signs and symptoms of opioid withdrawal can include sneezing, sweating, yawning, chills, **hyperventilation**, elevated body temperature, dilated pupils, muscle aches, vomiting, diarrhea, anxiety, and hostility.[2,3] Physical dependence occurs with other drugs (for example, the antihypertensive agents beta-blockers) as well as with opioids.[24]

In contrast to tolerance and physical dependence, which are pharmacologic conditions, **addiction** is a behavioral pattern that has genetic, psychosocial, and environmental factors influencing its development.[1,24,25] Addiction is defined as compulsive use of a drug despite physical harm and overwhelming involvement with its procurement and use.[1,24,25] The development of tolerance and physical dependence does not predict the risk of addiction.[1] In fact, while most patients chronically taking opioids for medical reasons develop tolerance and physical dependence, the risk of addiction is low.[3]

addiction (ă-dik′shŭn): a behavioral pattern that has genetic, psychosocial, and environmental factors influencing its development; compulsive use of a drug despite physical harm and overwhelming involvement with its procurement and use

Opioid Prescription and Regulation

Due to their potential for abuse, opioids are regulated as controlled substances in the United States under the Controlled Substances Act.[1] As shown in the following table, controlled substances are assigned to one of 5 schedules based on their potential for abuse.[26]

Schedules of Controlled Substances[26,27]

Schedule	I (CI)	II (CII)	III (CIII)	IV (CIV)	V (CV)
Abuse potential	High	High	Less than for I or II	Less than for III	Less than for IV
Accepted medical use	no	yes			
Prescriptions	—	Must be written (no oral), except in emergencies	May be written or oral		
Refills	—	None allowed (eg, patients must get a new prescription); however, physicians may write multiple prescriptions allowing ≤90 day supply with future dates on each prescription	May not be filled or refilled >6 months from the date of prescription; maximum refills without renewal is 5		

Challenges in Opioid Treatment

Despite the demonstrated and well-established efficacy of opioids, some physicians may be reluctant to prescribe opioids.

One reason is that prescribing opioids is more complex than prescribing other medications. Federal Drug Enforcement Agency (DEA) regulations include the following[26]:

- in order to prescribe opioids, a physician must register with the DEA and the registration must be renewed every 3 years
- the DEA specifies storage requirements for opioids and prescription blanks
- inventory and disposal records must be maintained and be available for inspection for at least 2 years

State agencies may impose additional regulations.[1] These can include programs that monitor opioid prescription patterns, with higher numbers of prescriptions or volume triggering further investigation.[24]

Some physicians may be reluctant to prescribe opioids and some patients may be reluctant to take opioids because of the fear of addiction.[3] However, research shows that physicians, patients, and their families frequently overestimate the risk of addiction, and often confuse physical dependence with addiction.[3]

Another reason some patients are reluctant to take opioids is because many assume it will affect motor function for skilled activities (eg, driving).[3] Patients are typically told to avoid driving or engaging in other skilled activities such as operating machinery when they first begin therapy with an opioid, or when they increase the dose.[3] However, these effects may diminish with ongoing treatment.[3]

2.6 Risk Assessment

Since abuse and misuse are possible with opioids, treatment guidelines for pain include a number of risk management strategies for opioid prescription.

The Universal Precautions in Pain Medicine developed by Gourlay and Heit is one example that provides a 10-step approach to the assessment and management of patients suffering from chronic pain.[28,29] The 10 steps are described in the following table.

Universal Precautions in Pain Medicine[28]
1. Make a diagnosis with appropriate differential: identify treatable causes and direct therapy to these causes; in their absence, treat symptoms
2. Conduct a psychological assessment including risk of addictive disorders: this can include urine drug testing
3. Informed consent: the physician needs to discuss the treatment and risks with the patient
4. Treatment agreement: a verbal or written treatment agreement should identify expectations and set boundaries
5. Pre- and post-intervention assessment of pain level and function: pain and function need to be assessed before and after therapy in order to determine its success
6. Appropriate trial of opioid therapy with or without adjunctive medications: opioids should not be considered a last resort, and therapy should be individualized for each patient
7. Reassessment of pain score and level of function: the patient should be regularly reassessed
8. Regularly assess the 4As of pain medication: routine assessment of analgesia, activity, adverse effects, and aberrant behavior
9. Periodically review pain diagnosis and comorbid conditions, including addictive disorders: disorders evolve over time, so ongoing evaluation is important
10. Documentation: careful records of the initial and ongoing evaluation is important for the patient's well-being and for legal reasons

Risk Assessment Tools

A common recommendation is that physicians assess each patient's risk for abusing opioids before prescribing these medications and during ongoing treatment.[10,24,28] A number of risk assessment tools are available to help physicians evaluate whether a patient is at risk for drug abuse or misuse. The following table briefly describes some of these tools, and examples of each are provided in the appendix to the module.

Tools Used to Assess a Patient's Risk for Abusing Opioids[10,30]	
Risk Assessment Tool	Description
Screener and Opioid Assessment for Patients With Pain® (SOAPP®)	▪ Designed to help physicians determine the level of monitoring that will be required ▪ Patients answer 14 questions (with a 5-point scale) that range in topics from problems with alcohol and drugs to mood swings and cravings for medication ▪ Patients are categorized based on total score, as either high-risk or low-risk
Opioid Risk Tool (ORT)	▪ Patient is assessed based on 5 questions that relate to family and personal history of substance abuse, history of preadolescent sexual abuse, and presence of psychological disease (eg, depression, schizophrenia) ▪ Based on total scores, patients are categorized as low-risk, moderate-risk, or high-risk
Diagnosis, Intractability, Risk Efficacy (D.I.R.E.)	▪ Patient assessed (3-point scale) on factors such as pain condition, previous treatments, presence of mental illness, reliability, social support, efficacy of treatment ▪ Based on total scores, patient is identified as suitable or unsuitable candidate for opioid therapy
Current Opioid Misuse Measure™ (COMM™)	▪ Designed to detect behaviors indicative of abuse or misuse ▪ Patient answers 17 questions (5-point scale) that relate to signs and symptoms of intoxication, emotional volatility, evidence of poor response to medications, addiction, healthcare-use patterns, and problematic medication behavior ▪ Total score identifies risk for misuse
CAGE-AID Screen	▪ Patient is asked 4 questions on drug or alcohol use ▪ Each affirmative response earns 1 point, with a total score of 1 = "possible problem"; 2 = "probable problem"

Treatment Agreement

Another common recommendation is that physicians ask patients who are about to start a trial of opioid therapy to sign a treatment agreement that helps set the boundaries for use.[24,28,31] In the treatment agreement, patients may promise that they will be honest with their physician about their drug history, that there will be no early prescription refills, and that they will undergo urine drug testing when requested.[10,24,31] The appendix to this module contains an example of a treatment agreement.

2.7 Summary of Common Opioids

The following table summarizes key facts regarding common short-acting opioids. Note that all are also available as generic products.

Common Short-Acting Opioids[32-34]

Generic Name	Common Formulations/Brand Names	Schedule
Codeine	▪ Solution and tablets as single agent; generic only	II
	▪ Solution, suspension, and tablets (plus acetaminophen, aspirin, or other agents): Tylenol® with Codeine	III, V
Fentanyl	▪ Intravenous: Sublimaze™ ▪ Buccal: Onsolis®, Actiq® ▪ Tablet: Fentora®	II
Hydrocodone	▪ Capsules, solution, and tablets (plus acetaminophen): Hydrocet®, Lortab® Elixir, Vicodin® ▪ Tablets (plus ibuprofen): Vicoprofen®	III
Hydromorphone	▪ Solution, tablets, injection, rectal suppositoires: Dilaudid®	II
Meperidine	▪ Solution, tablets, injection: Demerol®	II
Morphine	▪ Capsules, tablets, solution; IM, IV, and subcutaneous injection, rectal suppositories: Roxanol®, RMS®	II
Tapentadol	▪ Tablets: Nucynta®	II
Oxycodone	▪ Capsules, tablets, solution as single agent: Roxicodone®, OxyIR®, OxyFast™ ▪ Capsules, tablets, solution (plus acetaminophen): Tylox®, Percocet® ▪ Tablets (plus aspirin): Percodan®	II
Oxymorphone	▪ Tablets, injection: Opana®	II
Propoxyphene	▪ Capsules as single agent: Darvon® ▪ Tablets (plus acetaminophen): Wygesic™ ▪ Capsules (plus aspirin and caffeine): PC-CAP™	IV

The following table summarizes key facts regarding long-acting opioids. Section 3 profiles long-acting opioids in more detail.

Common Long-Acting Opioids[16,32,35-40]

Generic Name	Common Formulations/ Brand Names	Schedule
Fentanyl	▪ Transdermal: Duragesic®	II
Methadone	▪ Solution, tablets, injection: Dolophine®	II
Morphine	▪ Extended-release capsules: Kadian® ▪ Extended-release capsules: Avinza® ▪ Extended-release tablets: MS Contin® ▪ Morphine and naltrexone extended-release capsules: Embeda®	II
Oxycodone	▪ Controlled-release tablets: OxyContin®	II
Oxymorphone	▪ Extended-release tablets: Opana® ER	II

Summary

The following table summarizes the information presented in this section.

Opioids in Clinical Use
▪ Based on their interaction with opioid receptors, opioids can be classified as: – agonists: bind to receptors and stimulate them, producing analgesia; have no ceiling effect; examples include morphine and hydromorphone – partial agonists: bind to receptors and stimulate them, producing analgesia but are less active than full agonists; have a ceiling effect; example is buprenorphine – antagonists: bind to receptors and block the action of agonists; examples include naloxone and naltrexone – mixed agonist-antagonist: bind to and produce agonist effects at one type of receptor and antagonist effects at another type; example is pentazocine
▪ Potency: traditionally, morphine has been the standard against which all other opioids are compared – the equianalgesic dose or morphine equivalent is the dose needed to produce the same effect as 10 mg morphine parenterally or 30 mg or 60 mg morphine orally – hydromorphone is more potent than morphine
▪ Route of administration: opioids are available in oral (tablets, capsules, solutions), transmucosal (buccal, sublingual, nasal), parenteral (intravenous, intramuscular, subcutaneous), transdermal, and rectal formulations – fixed-dose combination products containing an opioid and one or more nonopioid analgesics are available
▪ Onset of action: primarily dependent on the route of administration, with speed greatest with intravenous→transmucosal→oral→transdermal
▪ Duration of action: except for methadone, all opioids are intrinsically short-acting, but some products are formulated in extended-release preparations that increase their duration of action – hydromorphone is a short-acting opioid; it is available outside the United States in a long-acting formulation (Jurnista™) that uses the OROS® Push-Pull™ osmotic delivery system ▪ an extended-release formulation using another delivery system (Palladone™) was briefly introduced in the United States but was removed due to safety concerns

(Cont'd)

Opioids in Clinical Use (Cont'd)

- Potential for abuse:
  - tolerance (a higher dose is needed to produce the same effect) and physical dependence (the body becomes adapted to the drug and needs it to function normally) are pharmacologic conditions distinct from addiction (compulsive use of a drug despite physical harm and overwhelming involvement in drug procurement and use)
  - due to their potential for abuse, opioids are regulated as controlled substances, assigned to 1 of 5 schedules
  - physicians may be reluctant to prescribe opioids due to the regulations involved in their prescription; physicians may be reluctant to prescribe opioids and patients may be reluctant to take them due to fears of addiction
    - risk of addiction is low with medical use of opioids
- Guidelines provide recommendations for responsible opioid prescription, including:
  - following the Universal Precautions in Pain Medicine
  - assessing each patient's risk for abuse
  - having patients sign a therapy agreement

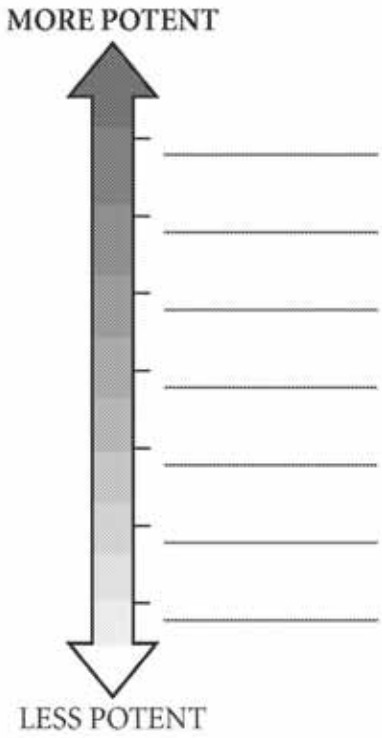
Progress Check

There may be **more than one** answer for each question.

1. Match each type of opioid with its description.

A ___ Opioid agonists	1 Bind to receptors and stimulate them, producing analgesia; have a ceiling effect
B ___ Opioid partial agonists	2 Bind to and produce agonist effects at one type of receptor and antagonist effects at another type
C ___ Opioid antagonists	3 Bind to receptors and stimulate them, producing analgesia; have no ceiling effect
D ___ Mixed opioid agonist-antagonists	4 Bind to receptors and block them

2. Identify the relative potency of the following opioids by labeling the figure with the following: hydromorphone, codeine, fentanyl, morphine, oxycodone, methadone, propoxyphene



Adapted from Brunton et al, 2006; Periyakoil et al, 2008.

3. What is the definition of an equianalgesic dose of an opioid?

   A The dose that produces equal effects when administered orally or parenterally

   B The dose that produces the same effect as the same milligram dose of morphine

   C The dose that produces the same effect as 10 mg morphine administered parenterally or 30 mg or 60 mg morphine administered orally

   D The morphine equivalent

4. List 5 administration routes for opioids.

   _____

   _____

   _____

   _____

   _____

5. Which administration route has the:

   A fastest onset of action? _____

   B slowest onset of action? _____

6. A short-acting opioid may be appropriate in which of the following situations?

   A Around-the-clock dosing

   B Initiation of therapy

   C Less frequent dosing is needed

   D As-needed dosing

7. Identify which agents have short-acting and long-acting formulations in the United States.

Agent	Short-Acting Formulation	Long-Acting Formulation
Codeine		
Fentanyl		
Methadone		
Hydromorphone		
Morphine		
Oxycodone		
Oxymorphone		

8. _____ means that the effectiveness of the drug diminishes over time, and a higher dose is necessary to produce the same effect.

A Physical dependence

B Psychologic dependence

C Tolerance

D Addiction

9. What schedule are the following opioids?

A Morphine: ___

B Hydromorphone: ___

C Codeine: ___

10. List 5 opioid risk assessment tools.

_____

_____

_____

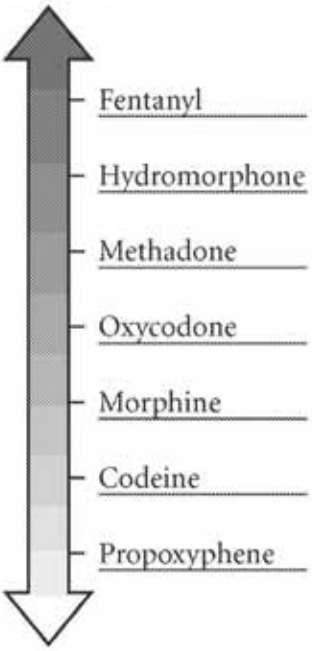
_____

_____

Answers

1. A 3; B 1; C 4; D 2

2. MORE POTENT



3. C, D

4.
- oral (tablets, capsules, solution)
- transmucosal (buccal, sublingual, nasal)
- parenteral (intravenous, intramuscular, subcutaneous)
- transdermal
- rectal

5. A intravenous

   B transdermal

6. B, D

7.

Agent	Short-Acting Formulation	Long-Acting Formulation
Codeine	X	
Fentanyl	X	X
Methadone		X
Hydromorphone	X	
Morphine	X	X
Oxycodone	X	X
Oxymorphone	X	X

8. C

9. A Morphine: II

B Hydromorphone: II

C Codeine: III or V

10. SOAPP®, ORT, D.I.R.E., COMM™, CAGE-AID Screen

3: Profiles of Long-Acting Opioids

Introduction

As noted in section 2, methadone is the only intrinsically long-acting opioid.[3] However, some short-acting opioids—such as morphine, oxycodone, oxymorphone, and fentanyl—are formulated in delivery systems that increase their duration of action, making them long-acting agents.[3,16] This section profiles the following long-acting agents:

- extended-release morphine formulations (MS Contin®, Kadian®, Avinza®, and Embeda®)
- extended-release oxycodone (OxyContin®)
- extended-release oxymorphone (Opana® ER)
- transdermal fentanyl (Duragesic®)

Learning Objectives

Upon completion of this section, you should be able to:

- State key features of long-acting opioids

3.1 Extended-Release Morphine

There are several branded and generic extended-release morphine products on the market, but the 4 branded agents that are most important for this discussion are:

- MS Contin® (morphine sulfate controlled-release tablets)/Purdue Pharma
- Kadian® (morphine sulfate extended-release capsules)/Actavis
- Avinza® (morphine sulfate extended-release capsules)/King Pharmaceuticals
- Embeda® (morphine sulfate and naltrexone hydrochloride extended-release capsules)/King Pharmaceuticals

All 4 agents have the same indication: management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[36-39] Furthermore, the indications note that these agents are[36-39]:

- not indicated for prn use
- not indicated in the immediate postoperative period for patients not previously taking this agent
- only indicated for postoperative use if the patient was already receiving the drug prior to surgery or if the pain is expected to be moderate to severe and persist for an extended period of time
- certain strengths are only indicated in opioid-tolerant patients

The following paragraphs provide more information about each of these products. Note that these agents are not bioequivalent, since the timing of release differs among the products.[36,37] That is, the slower release of morphine from Kadian® and Avinza® result in lower maximum but higher minimum plasma concentrations.[36,37]

MS Contin®

This product is available in tablet strengths of 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg morphine sulfate, but the 100 mg and 200 mg tablet strengths are for use in opioid tolerant patients only.[38] The tablets must be swallowed whole and must not be broken, chewed, dissolved, or crushed in order to prevent the rapid release of a potentially fatal dose.[38]

The package insert recommends that patients first receive an immediate-release opioid before receiving MS Contin®.[38] There is no standard dose of MS Contin®; instead, the initial dose is established based on the patient's existing opioid therapy.[38] For patients on immediate-release morphine, the package insert recommends administering one-half the patient's current 24-hour dose every 12 hours, or one-third every 8 hours.[38]

Following administration in normal volunteers, morphine is released gradually, with approximately 50% of the dose released after 1.5 hours.[38]

The package insert states that the most frequently observed adverse events are constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoria.[38,a]

Kadian®

This product is available in capsule strengths of 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg morphine sulfate, but the 100 mg and 200 mg capsule strengths are for use in opioid-tolerant patients only.[36] The capsules should be swallowed whole, and should not be chewed, crushed, or dissolved in order to prevent the rapid release of a potentially fatal dose.[36] The capsules can be opened and sprinkled on applesauce or administered through a gastrostomy tube.[36]

The package insert recommends that patients first receive an immediate-release opioid before receiving Kadian®.[36] There is no standard dose of Kadian®; instead, the initial dose is established based on the patient's existing opioid therapy.[36] For patients on immediate-release morphine, the package insert recommends administering one-half the patient's current 24-hour dose every 12 hours, or the total dose every 24 hours.[36]

[a] The description of most common adverse events has been adapted from each product's package insert.

The capsules contain polymer-coated pellets of morphine.[36] Following administration, morphine is released gradually, with approximately 50% of the dose released after 8 hours.[36]

The most common adverse events seen in clinical studies in patients with cancer pain were drowsiness, constipation, nausea, dizziness, and anxiety.[36]

Avinza®

This product is available in capsule strengths of 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 100 mg morphine sulfate, but the 45 mg, 60 mg, 75 mg, 90 mg, and 100 mg capsule strengths are for use in opioid-tolerant patients only.[37] The capsules should be swallowed whole, and should not be chewed, crushed, or dissolved in order to prevent the rapid release of a potentially fatal dose.[37] The package insert notes that patients cannot consume alcohol while taking Avinza®, because this could also result in the rapid release of a potentially fatal dose.[37] The capsules can be opened and sprinkled on applesauce or administered through a gastrostomy tube.[37]

There is no standard dose of Avinza®; instead, the initial dose is established based on the patient's existing opioid therapy.[37] For patients on immediate-release morphine, the package insert recommends administering the patient's current 24-hour dose once daily.[37]

Avinza® consists of 2 components: an immediate-release component that rapidly achieves a plateau morphine level, and an extended-release component that maintains the plasma levels throughout the 24-hour dosing period.[37]

The most common adverse events seen in clinical trials were constipation, nausea, somnolence, vomiting, and headache.[37]

Embeda®

Embeda® (morphine sulfate and naltrexone hydrochloride)/King Pharmaceuticals is a combination product consisting of morphine plus the opioid antagonist naltrexone in a ratio of 100 to 4.[39] It is the only product like this on the market, and was introduced in 2009.[39]

As described in section 2, opioid antagonists reverse the effects of opioid agonists.[3] As described in the Embeda® package insert, the administration of Embeda® resulted in decreased "drug liking" and euphoria compared to subjects receiving morphine alone.[39] However, the package insert also notes that the clinical significance of these results is unknown and there is no evidence of decreased abuse liability with Embeda®.[39]

Embeda® is available as capsules containing 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg of morphine and naltrexone.[39] The 100 mg/4 mg capsules are for opioid-tolerant patients only.[39] The capsules should be swallowed whole, or the contents of the capsules should be sprinkled on applesauce.[39] The pellets in the capsule should not be chewed, crushed, or dissolved before swallowing in order to prevent the rapid release of a potentially fatal dose.[39]

There is no standard dose of Embeda®. The package insert recommends that patients not previously on opioids be started on the lowest dose and titrated as necessary.[39] For patients on oral morphine, one-half the patient's total current daily opioid dose can be administered as Embeda every 12 hours, or the total dose every 24 hours.[39] The package insert provides general guidelines for converting patients on other opioids to Embeda®.[39]

Following administration to healthy volunteers, approximately 50% of the dose of morphine in the capsule reaches the circulation in 8 hours.[39]

The most common adverse events (≥10%) in phase 2 and 3 studies were constipation, nausea, and somnolence.[39] The following table lists adverse reactions >5% in a 12-week, placebo-controlled trial during the maintenance therapy portion of the trial.

Adverse Events >5% During Maintenance Therapy in a 12-Week, Placebo-Controlled Trial[39]

Adverse Event	Embeda® (n = 171)	Placebo (n = 173)
Constipation	7%	4%
Diarrhea	7%	7%
Nausea	11%	6%
General disorder and administration site conditions	5%	6%
Nervous system disorder	7%	6%
Psychiatric disorders	6%	5%

3.2 Extended-Release Oxycodone

An extended-release formulation of oxycodone is only available as the branded agent OxyContin® (oxycodone HCl controlled-release tablets)/Purdue Pharma.[32,40]

The indication for OxyContin® is similar to that of the extended-release morphine agents. OxyContin® is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[40] Furthermore, the indication notes that the agent is[40]:

- not indicated for prn use
- not indicated in the immediate postoperative period for patients not previously taking this agent
- only indicated for postoperative use if the patient was already receiving the drug prior to surgery or if the pain is expected to be moderate to severe and persist for an extended period of time

This product was originally available in tablet strengths of 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg oxycodone HCl.[40] However, the 160 mg tablet was voluntarily removed from the market because of concerns regarding abuse.[32] The 60 mg and 80 mg tablet strengths are for use in opioid-tolerant patients only.[40] The tablets should be swallowed whole, and should not be broken, chewed, or crushed in order to prevent the rapid release of a potentially fatal dose.[40]

There is no standard dose of OxyContin®; instead, the initial dose is established based on the patient's existing opioid therapy and using conversion factors provided in the package insert.[40] The package insert notes that the ratio for converting oral morphine to oral oxycodone is 0.5:1 (morphine:oxycodone).[40] It is administered twice daily.[40] For patients previously taking nonopioid analgesics, the package insert recommends a starting dose of 10 mg twice daily.[40]

Following administration to healthy volunteers, peak plasma concentrations are achieved in 2 to 3 hours after single doses of 10 mg to 80 mg.[40]

The following table lists the most common (>5%) adverse events reported by patients in clinical trials.

Most Common (>5%) Adverse Events in Clinical Trials[40]			
Adverse Event	OxyContin® (n = 227)	Immediate-Release Oxycodone (n = 225)	Placebo (n = 45)
Constipation	23%	26%	7%
Nausea	23%	27%	11%
Somnolence	23%	24%	4%
Dizziness	13%	16%	9%
Pruritus	13%	12%	2%
Vomiting	12%	14%	7%
Headache	7%	8%	7%
Dry mouth	6%	7%	2%
Asthenia	6%	7%	—
Sweating	5%	6%	2%

asthenia (as-thē′nē-ā): loss or lack of bodily strength; weakness; debility

3.3 Extended-Release Oxymorphone

An extended-release formulation of oxymorphone is only available as the branded agent Opana® ER (oxymorphone hydrochloride extended-release tablets)/Endo Pharmaceuticals.[16,32]

The indication for Opana® ER is similar to that of the extended release morphine agents. Opana® ER is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[16] Furthermore, the indication notes that the agent is[16]:

- not indicated for prn use
- not indicated in the immediate postoperative period for patients not previously taking this agent
- not indicated in the postoperative period if the pain is expected to be moderate to severe and persist for an extended period of time

This product is available in tablet strengths of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.[16] The tablets should be swallowed whole, and should not be broken, chewed, crushed or dissolved in order to prevent the rapid release of a potentially fatal dose.[16] The package insert notes that patients must not consume alcohol while taking Opana® ER, because this could also result in the rapid release of a potentially fatal dose.[16]

The recommended starting dose in opioid-naïve patients is 5 mg every 12 hours, and then titrated as needed every 3 to 7 days.[16] In opioid-experienced patients, the package insert recommends administering one-half the patient's total daily dose every 12 hours.[16] The package insert notes that the ratio for converting oral morphine to oral oxymorphone is 0.333:1 (morphine:oxymorphone).[16]

The following table lists the most common adverse events reported by patients in clinical placebo-controlled trials.

Most Common (>5%) Adverse Events in Placebo-Controlled Clinical Trials[16]

Adverse Event	Opana® ER (n = 1259)	Placebo (n = 461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness, excluding vertigo	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	1%
Sedation	6%	8%

3.4 Transdermal Fentanyl

Fentanyl is available as a transdermal patch as a generic and as the branded agent Duragesic® (fentanyl transdermal system)/PriCara.[32,35] It is available in the following strengths and patch sizes[35]:

- Duragesic®-12: contains 2.1 mg fentanyl in a 5.25 cm^2 patch
- Duragesic®-25: contains 4.2 mg fentanyl in a 10.5 cm^2 patch
- Duragesic®-50: contains 8.4 mg fentanyl in a 21 cm^2 patch
- Duragesic®-75: contains 12.6 mg fentanyl in a 31.5 cm^2 patch
- Duragesic®-100: contains 16.8 mg fentanyl in a 42 cm^2 patch

Duragesic® is indicated for the management of persistent, moderate to severe, chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time and that cannot be managed by other means such as NSAIDs, opioid combination products, or immediate-release opioids.[35] The indication further

states that it should only be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic®-25.[35] It is contraindicated for prn use, for postoperative or acute pain, for patients who are not opioid tolerant, or who require opioid analgesia for a short period of time.[35]

There is no standard dose of Duragesic®.[35] An equianalgesic dose for the transdermal formulation of fentanyl is not provided in most opioid equianalgesic dose conversion tables because of difficulties in translating oral or parenteral dosing to transdermal dosing. However, some data suggest that transdermal fentanyl is approximately 80 times more potent than oral morphine.[14] Instead, the initial dose is established based on the patient's existing opioid therapy, converting it to the equianalgesic dose of morphine, and using conversion tables provided in the package insert.[35] The patch should be placed on intact skin and can be worn for 72 hours.[35] The next patch should be placed on a different site.[35]

Following patch placement, the skin under the patch absorbs fentanyl and a depot concentrates in the upper skin layers; the drug then enters the systemic circulation.[35] Serum concentrations increase gradually, leveling off in 12 to 24 hours and then remaining relatively constant for the remainder of the 72-hour period.[35] After removal, concentrations decline gradually, falling approximately 50% in 20 to 27 hours.[35] This means that patients experiencing a serious adverse event with Duragesic® will need monitoring and treatment for at least 24 hours.[35]

Adverse events in adult patients in clinical trials (n = 380) included nausea, vomiting, constipation, dry mouth, somnolence, confusion, asthenia, sweating, abdominal pain, headache, fatigue, flu symptoms, anorexia, diarrhea, **dyspepsia**, dizziness, nervousness, hallucinations, anxiety, depression, euphoria, **dyspnea**, hypoventilation, **apnea**, pharyngitis, upper respiratory tract infection, pruritus, urinary retention.[35]

dyspepsia (dis-pep′sē-ā): indigestion

dyspnea (disp-nē′ā): shortness of breath

apnea (ap′nē-ā): absence of breathing

Summary

The following table summarizes information in this section.

Profiles of Long-Acting Opioids
▪ Methadone is the only intrinsically long-acting opioid, but some short-acting opioids (morphine, oxycodone, oxymorphone, and fentanyl)—are formulated in delivery systems that increase their duration of action, making them long-acting agents ▪ The long-acting opioids profiled in this section all have a similar indication: management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time; in addition: – they are not for prn use – not for use in the immediate postoperative period for patients not previously taking the agent – are only indicated for postoperative use if the patient was already receiving the drug prior to surgery or if the pain is expected to be moderate to severe and persist for an extended period of time – certain strengths are only indicated in opioid-tolerant patients

(Cont'd)

Profiles of Long-Acting Opioids (Cont'd)		
Agent	*Dosage Form/Strength*	*Administration Frequency*
Extended-release morphine[a]		
MS Contin® (morphine sulfate controlled-release tablets)/ Purdue Pharma	15 mg, 30 mg, 60 mg, 100 mg[b], and 200 mg[b] tablets	every 12 hours or every 8 hours
Kadian® (morphine sulfate extended-release capsules)/ Actavis	10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg[b], and 200 mg[b] capsules	every 12 hours or every 24 hours
Avinza® (morphine sulfate extended-release capsules)/ King Pharmaceuticals	30 mg, 45 mg[b], 60 mg[b], 75 mg[b], 90 mg[b], and 100 mg[b] capsules	every 24 hours
Embeda® (morphine sulfate and naltrexone hydrochloride)/ King Pharmaceuticals	morphine/naltrexone 20 mg/ 0.8 mg, 30 mg/1.2 mg, 50 mg/ 2 mg, 60 mg/2.4 mg, 80 mg/ 3.2 mg, and 100 mg/ 4 mg[b] capsules	every 12 hours or every 24 hours
Extended-release oxycodone		
OxyContin® (oxycodone HCl controlled-release tablets)/ Purdue Pharma	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg[b], and 80[b] mg tablets	every 12 hours
Extended-release oxymorphone		
Opana® ER (oxymorphone hydrochloride extended-release tablets)/ Endo Pharmaceuticals	5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets	every 12 hours
Transdermal fentanyl[a]		
Duragesic® (fentanyl transdermal system)/ PriCara	▪ Duragesic®-12: 2.1 mg in a 5.25 cm^2 patch[b] ▪ Duragesic®-25: 4.2 mg in a 10.5 cm^2 patch[b] ▪ Duragesic®-50: 8.4 mg in a 21 cm^2 patch[b] ▪ Duragesic®-75: 12.6 mg in a 31.5 cm^2 patch[b] ▪ Duragesic®-100: 16.8 mg in a 42 cm^2 patch[b]	patch is applied to intact skin and can remain on for 72 hours

[a] Generics also available.
[b] Opioid-tolerant doses.

Progress Check

There may be **more than one** answer for each question.

1. Match each brand name with its generic component.

A	___ Duragesic®	1	Morphine
B	___ Kadian®	2	Morphine plus naltrexone
		3	Oxycodone
C	___ OxyContin®	4	Fentanyl
D	___ Opana® ER	5	Oxymorphone
E	___ Embeda®		

2. Which of the following is (are) **true** regarding the indication for these long-acting opioids?

   A Each agent has a distinct indication that has helped to establish its niche in the market.

   B All the agents are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

   C All the agents are indicated for prn use.

   D None of the agents are indicated for mild pain.

Answers

1. A 4; B 1; C 3; D 5; E 2
2. B, D

Summary

1: Physiologic Effects of Opioids

The 3 types of opioid receptors known to be involved in analgesia are:

- μ opioid receptors
- δ opioid receptors
- κ opioid receptors

Most clinically available opioids produce analgesia primarily by binding to μ receptors in the CNS. The effects associated with opioid binding at μ receptors include analgesia as well as other physiologic effects.

When opioids bind to μ opioid receptors, they close calcium channels on the presynaptic neuron (reducing the release of neurotransmitters) and open potassium channels on the postsynaptic neuron (making it more difficult for an impulse to be created). These actions mean that:

- in the brain, opioids activate neurons that send inhibitory signals to neurons in the spinal cord
- in the spinal cord, opioids inhibit neurons that transmit pain impulses from the spinal cord to the brain

Key physiologic effects of opioids include the following:

- opioids are the most potent pain-relieving drugs available, and morphine remains the standard against which strong analgesics are compared
- opioids can cause respiratory depression by decreasing the breathing rate and depth of each breath in a dose-related fashion; rarely clinically significant in otherwise healthy people taking typical therapeutic doses
- patients can experience euphoria or dysphoria
- miosis occurs with almost all opioids
- sedation, drowsiness, and cognitive effects are common, especially when therapy is initiated or the dose is increased
- the cough reflex can be suppressed
- opioids decrease the wave-like movements of the intestine, which slows gastric emptying time, which may result in constipation
- opioids inhibit the urinary voiding reflex and increase smooth muscle tone of the ureter and bladder, which can result in urinary retention
- pruritus can occur due to opioid effects in the CNS as well as because of peripheral histamine release
- nausea and vomiting can occur due to opioid stimulation of the brain's vomiting center and effects in the GI tract

2: Opioids in Clinical Use

Based on their interaction with opioid receptors, opioids can be classified as:

- agonists: bind to receptors and stimulate them, producing analgesia; have no ceiling effect; examples include morphine and hydromorphone
- partial agonists: bind to receptors and stimulate them, producing analgesia but are less active than full agonists; have a ceiling effect; example is buprenorphine
- antagonists: bind to receptors and block the action of agonists; examples include naloxone and naltrexone
- mixed agonist-antagonist: bind to and produce agonist effects at one type of receptor and antagonist effects at another type; example is pentazocine

Opioids are classified by a variety of factors, including potency, route of administration, onset and duration of action, and potential for abuse.

In terms of potency, traditionally, morphine has been the standard against which all other opioids are compared. The equianalgesic dose or morphine equivalent is the dose needed to produce the same effect as 10 mg morphine parenterally or 30 mg or 60 mg morphine orally. Note that hydromorphone is more potent than morphine—the ratio is 5:1 morphine:hydromorphone.

In terms of route of administration, opioids are available in oral (tablets, capsules, solutions), transmucosal (buccal, sublingual, nasal), parenteral (intravenous, intramuscular, subcutaneous), transdermal, and rectal formulations. They are also available in fixed-dose combination products containing an opioid and one or more nonopioid analgesics.

Onset of action primarily is dependent on the route of administration, with speed greatest with intravenous→transmucosal→oral→transdermal. In terms of duration of action, except for methadone, all opioids are intrinsically short-acting, but some products are formulated in extended-release preparations that increase their duration of action. Hydromorphone is a short-acting opioid; it is available outside the United States in a long-acting formulation (Jurnista™) that uses the OROS® Push-Pull™ osmotic delivery system. An extended-release formulation using another delivery system (Palladone™) was briefly introduced in the United States but was removed due to safety concerns.

Opioids are also classified by their potential for abuse. Tolerance (a higher dose is needed to produce the same effect) and physical dependence (the body becomes adapted to the drug and needs it to function normally) are pharmacologic conditions distinct from addiction, which is compulsive use of a drug despite physical harm and overwhelming involvement in drug procurement and use. Due to their potential for abuse, opioids are regulated as controlled substances and assigned to one of 5 schedules. Physicians may be reluctant to prescribe opioids due to the regulations involved in their prescription. Because of fears of addiction, physicians may be reluctant to prescribe opioids and patients may be reluctant to take them. However, the risk of addiction is low with medical use of opioids. Guidelines provide recommendations for responsible opioid prescription, including:

- following the Universal Precautions in Pain Medicine
- assessing each patient's risk for abuse
- having patients sign a therapy agreement

3: Profiles of Long-Acting Opioids

Methadone is the only intrinsically long-acting opioid, but some short-acting opioids (morphine, oxycodone, oxymorphone, and fentanyl)—are formulated in delivery systems that increase their duration of action, making them long-acting agents.

The long-acting opioids profiled in this section all have a similar indication: management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. They are not for prn use, not for use in the immediate postoperative period for patients not previously taking the agent, are only indicated for postoperative use if the patient was already receiving the drug prior to surgery or if the pain is expected to be moderate to severe and persist for an extended period of time, and certain strengths are only indicated for opioid-tolerant patients.

Multiple generic forms of extended-release morphine are available; branded agents include:

- MS Contin® (morphine sulfate controlled-release tablets)/Purdue Pharma; it is generally administered every 12 hours or every 8 hours
- Kadian® (morphine sulfate extended-release capsules)/Actavis; it is administered every 12 hours or every 24 hours
- Avinza® (morphine sulfate extended-release capsules)/King Pharmaceuticals; it is administered every 24 hours
- Embeda® (morphine sulfate and naltrexone hydrochloride)/King Pharmaceuticals; it is administered every 12 hours or every 24 hours

For extended-release oxycodone, only the branded agent is available: OxyContin® (oxycodone HCl controlled-release tablets)/Purdue Pharma. It is administered every 12 hours.

For extended-release oxymorphone, only the branded agent is available: Opana® ER (oxymorphone hydrochloride extended-release tablets)/ Endo Pharmaceuticals. It is administered every 12 hours.

For transdermal fentanyl, generics are available; a key branded agent is Duragesic® (fentanyl transdermal system)/PriCara. The patch is applied to intact skin and can remain on for 72 hours.

Glossary

addiction
(ă-dik′shŭn)..... a behavioral pattern that has genetic, psychosocial, and environmental factors influencing its development; compulsive use of a drug despite physical harm and overwhelming involvement with its procurement and use[1,24,25]

afferent neurons
(af′ĕr-ĕnt nū′rons)..... also called sensory neurons; detect and/or transmit information from the PNS to the CNS[8]

agonist
(ag′on-ist)..... a drug capable of initiating drug actions by combining with a receptor[41]

analgesia
(an′ăl-jē′zē-ă)..... relief of pain[41]

antagonist
(an-tag′ŏ-nist)..... a drug that binds to receptors and blocks the binding and action of agonists at the receptor[41]

apnea
(ap′nē-ă)..... absence of breathing[41]

asthenia
(as-thē′nē-ă)..... loss or lack of bodily strength; weakness; debility[41]

bolus
(bō′lŭs)..... a single, relatively large quantity of a drug[41]

ceiling effect..... occurs when increasing the dose of a drug above a certain point does not produce a further increase in response[3]

central nervous system (CNS)
(sen′trăl ner′vŭs sis′tĕm)..... the brain and the spinal cord[8]

dyspepsia
(dis-pep′sē-ă)..... indigestion[41]

dysphoria
(dis-fōr′ē-ă) ..... mood of general dissatisfaction, restlessness, depression, and anxiety; a feeling of unpleasantness or discomfort[41]

dyspnea
(disp-nē′ă) ..... shortness of breath[41]

endorphins
(en-dōr′finz) ..... group of endogenous opioid peptides in the body[41]

enkephalin
(en-kef′ă-lin) ..... a type of endorphin, which are endogenous opioid peptides in the body[41]

equianalgesic
(e′kwē-anal-jē′zik) ..... the dose of a drug needed to produce the same amount of pain relief as a 10 mg intravenous or a 30 mg oral dose of morphine; often termed a morphine equivalent[1,3]

euphoria
(yū-fōr′ē-ă) ..... a feeling of pleasure or well-being, commonly exaggerated and not necessarily well-founded; may be induced by a drug or substance of abuse[41]

gamma-aminobutyric acid (GABA)
(gam′ă ă-mē′nō- byū-tir′ik as′id) ..... a major inhibitory neurotransmitter in the brain[8]

glutamate
(glū′tă-māt) ..... a major excitatory neurotransmitter[8]

histamine
(his′tă-mēn) ..... a monoamine neurotransmitter; in the periphery, it is released from cells in the immune system; it also stimulates gastric secretion and the constriction of bronchial smooth muscle[41]

hyperventilation (hī′pĕr-ven′ti-lā′shŭn)	increased pulmonary rate that is greater than necessary for gas exchange; can lead to dizziness, fainting, psychomotor impairment[9]
miosis (mī-ō′sis)	constriction of the pupil of the eye, resulting from a normal response to an increase in light or caused by certain drugs or pathologic conditions[41]
parenteral (pă-ren′tĕr-ăl)	administration by some other route than through the gastrointestinal tract; particularly refers to administration via injection[41]
partial agonist (ag′on-ist)	an agent that binds to receptors and stimulates them, but has less activity compared to a full agonist[3]
peripheral nervous system (PNS) (pĕ-rif′ĕr-ăl)	all nervous system tissue except for the brain and spinal cord[8]
physical dependence	the body's normal adaptation to the opioid, and the body requires continued drug administration in order to function normally[1,24]
prn	as needed (from the Latin for *pro re nata*, which means as the occasion arises)[41]
pruritus (prū-rī′tŭs)	itching[41]
substance P (sŭb′stănts)	neurotransmitter found in inflamed tissue and involved in pain transmission[41]
supra-therapeutic dose	a dose greater than that needed to produce a desired effect[9]

synergism (sin′ĕr-jizm)	coordinated or correlated action of 2 or more structures, agents, or physiologic processes so that the combined action is greater than the sum of each acting separately[41]
tolerance (tol′ĕr-ăns)	the effectiveness of the drug diminishes over time, and a higher dose is necessary to produce the same effect that was previously attained at a lower dose[24]
urinary retention (yūr′i-nār′ē rē-ten′shŭn)	the keeping of urine in the body that should normally be discharged[41]

Appendix

The following pages are examples of opioid risk assessment tools and a patient opioid agreement. They include:

- Screener and Opioid Assessment for Patients with Pain® (SOAPP®)
- Opioid Risk Tool (ORT)
- Diagnosis, Intractability, Risk Efficacy (D.I.R.E.)
- Current Opioid Misuse Measure™ (COMM™)
- CAGE-AID Screen for Alcohol/Substance Abuse or Dependence
- Long-term Controlled Substances Therapy for Chronic Pain Sample Agreement

Screener and Opioid Assessment for Patients with Pain® (SOAPP®) Version 1.0-14Q

Name: _____ Date: _____

The following are some questions given to all patients at the Pain Management Center who are on or being considered for opioids for their pain. Please answer each question as honestly as possible. This information is for our records and will remain confidential. Your answers alone will not determine your treatment. Thank you.

Please answer the questions below using the following scale:

0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

1.	How often do you have mood swings?	0	1	2	3	4
2.	How often do you smoke a cigarette within an hour after you wake up?	0	1	2	3	4
3.	How often have any of your family members, including parents and grandparents, had a problem with alcohol or drugs?	0	1	2	3	4
4.	How often have any of your close friends had a problem with alcohol or drugs?	0	1	2	3	4
5.	How often have others suggested that you have a drug or alcohol problem?	0	1	2	3	4
6.	How often have you attended an AA or NA meeting?	0	1	2	3	4
7.	How often have you taken medication other than the way that it was prescribed?	0	1	2	3	4
8.	How often have you been treated for an alcohol or drug problem?	0	1	2	3	4
9.	How often have your medications been lost or stolen?	0	1	2	3	4
10.	How often have others expressed concern over your use of medication?	0	1	2	3	4
11.	How often have you felt a craving for medication?	0	1	2	3	4
12.	How often have you been asked to give a urine screen for substance abuse?	0	1	2	3	4
13.	How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years?	0	1	2	3	4
14.	How often, in your lifetime, had you had legal problems or been arrested?	0	1	2	3	4

Please include any additional information you wish about the above answers. Thank you.

Adapted from Chou et al, 2009.

Date _____

Patient Name _____

OPIOID RISK TOOL (ORT)

			Mark each box that applies	Item Score If Female	Item Score If Male
1.	**Family history of substance abuse**	Alcohol	[ ]	1	3
		Illegal Drugs	[ ]	2	3
		Prescription Drugs	[ ]	4	4
2.	**Personal History of Substance Abuse**	Alcohol	[ ]	3	3
		Illegal Drugs	[ ]	4	4
		Prescription Drugs	[ ]	5	5
3.	**Age (Mark box if 16 – 45)**		[ ]	1	1
4.	**History of Preadolescent Sexual Abuse**		[ ]	3	0
5.	**Psychological Disease**	Attention Deficit Disorder	[ ]	2	2
		Obsessive Compulsive Disorder			
		Bipolar			
		Schizophrenia			
		Depression	[ ]	1	1
TOTAL			[ ]		
Total Score Risk Category		Low Risk 0 – 3	Moderate Risk 4 – 7		High Risk ≥8

Adapted from Chou et al, 2009.

D.I.R.E. Score: Patient Selection for Chronic Opioid Analgesia

For each factor, rate the patient's score from 1-3 based on the explanations in the right hand column

Score	Factor	Explanation
	Diagnosis	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, non-specific back pain. 2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain. 3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.
	Intractability	1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process. 2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness). 3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.
	Risk	(R= Total of P+C+R+S below)
	Psychological:	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues. 2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder. 3 = Good communication with clinic. No significant personality dysfunction or mental illness.
	Chemical Health:	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse. 2 = Chemical coper (uses medications to cope with stress) or history of CD in remission. 3 = No CD history. Not drug-focused or chemically reliant.
	Reliability:	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through. 2 = Occasional difficulties with compliance, but generally reliable. 3 = Highly reliable patient with meds, appointments & treatment.
	Social Support:	1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles. 2 = Reduction in some relationships and life roles. 3 = Supportive family/close relationships. Involved in work or school and no social isolation.
	Efficacy score	1 = Poor function or minimal pain relief despite moderate to high doses. 2 = Moderate benefit with function improved in a number of ways (or insufficient info- hasn't tried opioid yet or very low doses or too short of a trial). 3 = Good improvement in pain and function and quality of life with stable doses over time.

_____Total score = D + I + R + E

Score 7-13: Not a suitable candidate for long-term opioid analgesia
Score 14-21: Good candidate for long-term opioid analgesia

Adapted from Chou et al, 2009.

Current Opioid Misuse Measure™ (COMM™)

Please answer each question as honestly as possible. Keep in mind that we are only asking about the **past 30 days**. There are no right or wrong answers. If you are unsure about how to answer the question, please give the best answer you can.

Please answer the questions using the following scale:	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. In the past 30 days, how often have you had trouble with thinking clearly or had memory problems?	O	O	O	O	O
2. In the past 30 days, how often do people complain that you are not completing necessary tasks? (ie, doing things that need to be done, such as going to class, work, or appointments)	O	O	O	O	O
3. In the past 30 days, how often have you had to go to someone other than your prescribing physician to get sufficient pain relief from medications? (ie, another doctor, the Emergency Room, friends, street resources)	O	O	O	O	O
4. In the past 30 days, how often have you taken your medications differently from how they are prescribed?	O	O	O	O	O
5. In the past 30 days, how often have you seriously thought about hurting yourself?	O	O	O	O	O
6. In the past 30 days, how much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc)?	O	O	O	O	O
7. In the past 30 days, how often have you been in an argument?	O	O	O	O	O
8. In the past 30 days, how often have you had trouble controlling your anger (eg, road rage, screaming, etc)?	O	O	O	O	O
9. In the past 30 days, how often have you needed to take pain medications belonging to someone else?	O	O	O	O	O
10. In the past 30 days, how often have you been worried about how you're handling your medications?	O	O	O	O	O
11. In the past 30 days, how often have others been worried about how you're handling your medications?	O	O	O	O	O
12. In the past 30 days, how often have you had to make an emergency phone call or show up at a clinic without an appointment?	O	O	O	O	O
13. In the past 30 days, how often have you gotten angry with people?	O	O	O	O	O
14. In the past 30 days, how often have you had to take more of your medication than prescribed?	O	O	O	O	O
15. In the past 30 days, how often have you borrowed pain medication from someone else?	O	O	O	O	O
16. In the past 30 days, how often have you used your pain medicine for symptoms other than for pain (eg, to help you sleep, improve your mood, or relieve stress)?	O	O	O	O	O
17. In the past 30 days, how often have you had to visit the Emergency Room?	O	O	O	O	O

Adapted from Chou et al, 2009.

CAGE-AID Screen for Alcohol/Substance Abuse or Dependence

The CAGE-AID Screen broadens the CAGE to include other drug use.

CAGE-AID Screen

Have you ever:

- C felt you ought to **cut** down on your drinking *(or drug use)*?
- A had people **annoy** you by criticizing your drinking *(or drug use)*?
- G felt bad or **guilty** about your drinking *(or drug use)*?
- E had a drink *(or drug use)* as an **eye opener** first thing in the morning to steady your nerves or get rid of a hangover or to get the day started?

Adapted from Institute for Clinical Systems Improvement, 2008.

Long-term Controlled Substances Therapy for Chronic Pain

A consent form from the American Academy of Pain Medicine

The purpose of this agreement is to protect your access to controlled substances and to protect our ability to prescribe for you.

The long-term use of such substances as opioids (narcotic analgesics), benzodiazepine tranquilizers, and barbiturate sedatives is controversial because of uncertainty regarding the extent to which they provide long-term benefit. There is also the risk of an addictive disorder developing or of relapse occurring in a person with a prior addiction. The extent of this risk is not certain.

Because these drugs have potential for abuse or diversion, strict accountability is necessary when use is prolonged. For this reason the following policies are agreed to by you, the patient, as consideration for, and a condition of, the willingness of the physician whose signature appears below to consider the initial and/or continued prescription of controlled substances to treat your chronic pain.

1. All controlled substances must come from the physician whose signature appears below or, during his or her absence, by the covering physician, unless specific authorization is obtained for an exception. (Multiple sources can lead to untoward drug interactions or poor coordination of treatment.)
2. All controlled substances must be obtained at the same pharmacy, where possible. Should the need arise to change pharmacies, our office must be informed. The pharmacy that you have selected is:

   _____ phone: _____.
3. You are expected to inform our office of any new medications or medical conditions, and of any adverse effects you experience from any of the medications that you take.
4. The prescribing physician has permission to discuss all diagnostic and treatment details with dispensing pharmacists or other professionals who provide your health care for purposes of maintaining accountability.
5. You may not share, sell, or otherwise permit others to have access to these medications.
6. These drugs should not be stopped abruptly, as an abstinence syndrome will likely develop.
7. Unannounced urine or serum toxicology screens may be requested, and your cooperation is required. Presence of unauthorized substances may prompt referral for assessment for addictive disorder.

8. Prescriptions and bottles of these medications may be sought by other individuals with chemical dependency and should be closely safeguarded. It is expected that you will take the highest possible degree of care with your medication and prescription. They should not be left where others might see or otherwise have access to them.

9. Original containers of medications should be brought in to each office visit.

10. Since the drugs may be hazardous or lethal to a person who is not tolerant to their effects, especially a child, you must keep them out of reach of such people.

11. Medications may not be replaced if they are lost, get wet, are destroyed, left on an airplane, etc. If your medication has been stolen and you complete a police report regarding the theft, an exception may be made.

12. Early refills will generally not be given.

13. Prescriptions may be issued early if the physician or patient will be out of town when a refill is due. These prescriptions will contain instructions to the pharmacist that they not be filled prior to the appropriate date.

14. If the responsible legal authorities have questions concerning your treatment, as might occur, for example, if you were obtaining medications at several pharmacies, all confidentiality is waived and these authorities may be given full access to our records of controlled substances administration.

15. It is understood that failure to adhere to these policies may result in cessation of therapy with controlled substance prescribing by this physician or referral for further specialty assessment.

16. Renewals are contingent on keeping scheduled appointments. Please do not phone for prescriptions after hours or on weekends.

17. It should be understood that any medical treatment is initia lly a trial, and that continued prescription is contingent on evidence of benefit.

18. The risks and potential benefits of these therapies are explained elsewhere [and you acknowledge that you have received such explanation].

19. You affirm that you have full right and power to sign and be bound by this agreement, and that you have read, understand, and accept all of its terms.

Physician Signature	Patient Signature
Date	Patient Name (Printed)

Approved by the AAPM Executive Committee on April 2, 2001.

Adapted from Chou et al, 2009.

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